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Dear Dr Henney,

Ref: 21 CFR Part 201

**Requirements on content and format of labeling from human prescription drugs and biologics; requirements for Prescription Drug Product labels**

I am delighted to see a change in the definition of an ADR. The previous definitions were inappropriate.

I note that on page 81120 para (9) 8 *Listing of adverse reactions* that 'must list the adverse reactions (not all the adverse events) that occur with the drug...' Does this mean the end of tables with AEs that 'do not appear at increased frequency compared to placebo....' If so, this is a very welcome change and will force companies to assess AEs for causality.

On page 81120 you suggest that ADRs may be categorised... by severity of the reaction and later 'An AR that is significantly more severe than the other reactions listed in the category....' I believe that the word 'severe' is inappropriate for the following reasons:

- 1) There is no agreed definition of 'severe' despite several possibilities: Tangrea *et al*, 1991; Assenzo and Sho, 1982; Grohmann *et al*, 1989.
- 2) The term is frequently subjective and, therefore, there is no possibility of comparing severity
- 3) It is extremely rare that the term 'severe' can be applied to all the reactions of a certain class of ADR. Usually only a few are severe ~~the~~ most being mild or moderate.
- 4) The pharmaceutical companies do not use the term unless forced to do so, usually by a regulatory authority.

I would suggest that the word 'serious' despite its regulatory definition would be more suitable.

**References**

Tangrea J.A., Adrianza, M.E., and Mac Adams, M. (1991) A method for the detection and management of adverse events in clinical trials. *Drug Inf J.* 25, 63-80.

Assenzo, J.R. and Sho V.S. (1982) Use of statistics in the analysis of side-effect data from clinical trials of psychoactive agents. *Prog Neuropsychopharmacol Biol Psychiat*, 6, 543-550

Grohmann, Rr., Rutter, E., and Schmidt, L.G. (1989) Adverse effects of clozapine. *Psychopharm*, 99, S101-S104.

Yours faithfully

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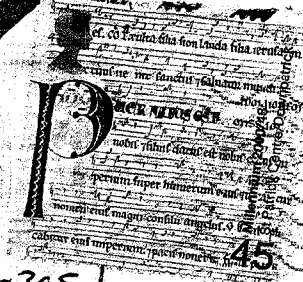
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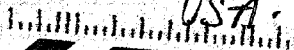


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